

The primordial thymus

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exerted by AhR is somehow more prevalent than the one exerted by enzymes generating its physiologic ligands, e.g., L-kynurenine. There are at least two possible and non-mutually exclusive explanations for this. The first is that the enzymes involved in tryptophan catabolism are to some extent redundant in their ability to produce the AhR ligand L-kynurenine. Alternatively, it is possible that additional AhR ligand(s) are produced physiologically via other host catabolic pathways that support the protective effects of AhR. Candidate AhR ligands include those produced by heme oxygenases (HOs), a stress-responsive enzyme that confers disease tolerance to polymicrobial infection (Larsen et al., 2010). Heme catabolism by HOs produces several putative AhR ligands including biliverdin (a direct end-product of HO activity) and bilirubin (a potent antioxidant generated from biliverdin catabolism by biliverdin reductase that activates AhR) (Denison and Nagy, 2003). Moreover, heme catabolism by HOs also generates carbon monoxide, a gas-transmitter that can bind ferrous (Fe^{2+}) iron contained in the heme group of AhR

and modulate its activity. Whether regulation of disease tolerance by AhR acts via a mechanism involving the putative action of different end products of heme catabolism by HOs has not been established. If proven correct, this would argue for the integration of the AhR signal transduction pathways in a wider network of stress-responsive signaling pathways regulating disease tolerance to infection.

Although simple in its essence, the concept of disease tolerance should have major implications to our current understanding of the pathogenesis of infectious diseases. The study by Bessede et al. (2014) and future studies should provide the mechanistic insight, i.e., “nuts and bolts,” allowing for targeting this defense strategy therapeutically toward a much-needed supplement to the current clinical approaches available in the treatment of infectious diseases.

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The Primordial Thymus: Everything You Need Under One Roof

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Lymphocytes normally develop within anatomically distinct tissues. In *Cell Reports*, Swann et al. (2014) reconstruct the primordial thymus and suggest that it was a site of combined T and B lymphopoiesis before evolving into an organ specialized for T cell production.

Through random recombination of gene segments encoding antigen receptors, lymphocytes recognize a wide range of pathogens and represent key players in adaptive immunity. They are also heterogeneous: B cells produce antibodies recognizing antigen in its native form, while $\alpha\beta$ T cells recognize antigenic peptides via major histocompatibility

complexes (MHC). In vertebrates, this lymphocyte heterogeneity is mirrored in the tissues that support their generation. Thus, bursectomy and thymectomy experiments in birds showed antibody-producing cells, and cytotoxic lymphocytes arose in anatomically distinct sites (Cooper et al., 1966). Significantly, studies on jawless vertebrates show that the

specialized T lymphopoietic role of the thymus is ancient. For example, epithelial regions of developing lamprey gill structures express *Foxn1* (Bajoghli et al., 2011) encoding a transcription factor essential for thymic epithelial cell (TEC) development. Moreover, these tissues contained lymphocytes with features of T cells (e.g., expression of variable

lymphocyte receptors type A [VLRA] and VLRC-type antigen receptors), but not B cells (VLRB-type antigen receptors). Thus, the anatomical separation of sites supporting lymphocyte production has existed for over 500 million years. In a recent issue of *Cell Reports*, by manipulating expression of *Foxn1* and its ancient paralogue *Foxn4* in the context of vertebrate thymus development, Swann et al. (2014) discover that the primordial thymus represented a site that fostered both T and B cell development. Such findings are significant because they reveal the emergence of specialization in lymphoid tissues and suggest how the thymus developed away from a common site of lymphopoiesis toward a site specialized for T cell development.

To investigate the evolutionary origins of thymic tissue, Swann et al. (2014) analyzed the thymus of vertebrates (mouse), cartilaginous fish (catshark), and bony fish (zebrafish and medaka) for *Foxn1* and *Foxn4* expression, the latter an ancient gene that gave rise to *Foxn1* by duplication. While expression of both genes was readily detectable in fish, *Foxn4* was barely detectable in mouse thymus. Such findings suggested to the authors that TEC expression of *Foxn4* was progressively lost during evolution, a scenario consistent with the lack of detectable *Foxn4* in the thymus of jawless vertebrates. Moreover, while *Foxn4* cannot compensate for the absence of *Foxn1* in mice, further experiments showed the opposite: that *Foxn4*-mediated thymus development in teleost fish occurs in the absence of *Foxn1*. Such findings define an important functional role for the ancient gene *Foxn4* during thymus development in early vertebrates, prior to the gene duplication giving rise to *Foxn1*. Next, the authors adopted a transgenic approach in which either *Foxn1* or *Foxn4* expression was introduced into nude mice, which lack normal thymus development due to disruption of the endogenous *Foxn1*. As expected,

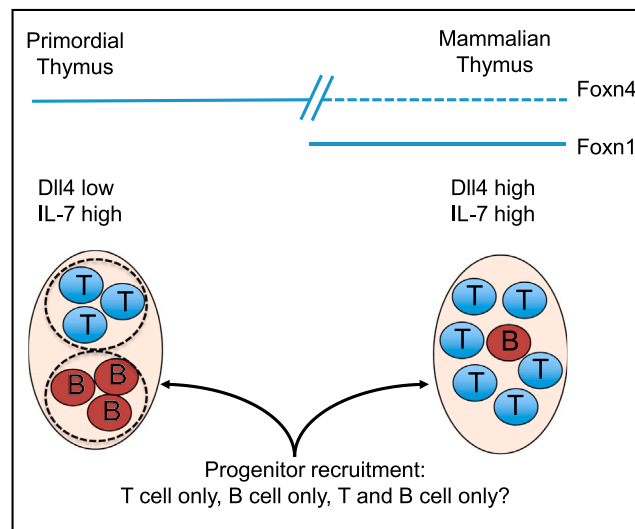


Figure 1. Emergence of Thymus Specialization for T Cell Development from a Dual-Functioning Lymphoid Organ

In the primordial thymus, expression of *Foxn4* results in conditions (DLL4 low, IL-7 high) that are favorable for compartmentalized T and B lymphopoiesis. Following the emergence of *Foxn1* by gene duplication, expression of *Dll4* increased leading to an environment that favors T lymphopoiesis over B lymphopoiesis. While such changes correlate in the ability of the thymus to support T and B lymphopoiesis, the nature of thymus-colonizing cells and the ability of the thymus to impose or reveal T cell potential, remain unclear.

reintroduction of *Foxn1* rescued thymus development in nude mice. Most striking was the impact of introducing *Foxn4* in the context of *Foxn1* deficiency. Here, thymus development occurred, including the generation of cortical and medullary TEC that supported $\alpha\beta$ T cell development. Yet, restoring thymic function via *Foxn4* was accompanied by an increase in the numbers of intrathymic B cells, including immature progenitors typically found in bone marrow. Interestingly, developing B cells were found in thymic areas distinct to those housing T cell progenitors. To explain these observations, Swann et al. (2014) examined expression of genes in the *Foxn4* transgenic mouse thymus that either represent specific regulators of T cell development (*Dll4*) or are involved in both T and B cell development (*Il7*). Expression of *Dll4*, a FOXN1-dependent gene (Calderón and Boehm, 2012), was reduced while expression of *Il7*, a FOXN1-independent gene (Zamisch et al., 2005), was unaltered, collectively generating intrathymic conditions (high interleukin-7 [IL-7], low DLL4) permissive for B cell development (Figure 1). Thus, by manipulating expression of the *Foxn1* and *Foxn4* gene family to mimic expression patterns that emerged during

evolution, Swann et al. (2014) report the reconstruction of the primordial thymus and show that it represents a tissue with dual T and B lymphopoietic function.

The study of Swann et al. (2014) is important in several respects, including understanding the current specialization of the thymus for T cell development. While the thymus represents the unique site for T cell production in all vertebrates, several tissues share the capacity to support B cell development. That the primordial thymus represented a site of combined lymphopoietic activity suggests that changes in expression of the *Foxn1* and *Foxn4* gene family, notably the gene duplication that generated *Foxn1*, limited the ability of the thymus to support B cell development. Thus, high amounts of FOXN1-dependent

Dll4 increased the T lymphopoietic properties of the thymus at the expense of B lymphopoiesis. This is compatible with studies demonstrating that when the NOTCH-DLL4 axis is compromised, there is an increased ability of the thymus to support B cell development (Shah and Zúñiga-Pflücker, 2014). Relevant to this is comparison of the microenvironmental requirements of T and B lymphopoiesis. While the latter requires stromal support from mesenchyme, the former requires a combination of both mesenchymal and epithelial interactions (Anderson et al., 1993). Thus, the increasing efficacy of intrathymic T cell development caused by the appearance of *Foxn1* might have led to increased competition for mesenchyme support between developing T and B cell progenitors, and the progressive decline in B lymphopoiesis. Whatever the mechanism that caused restriction of the dual lymphopoietic properties of the thymus, it is still not clear how this process led to the fetal liver and bone marrow emerging as sites of B cell development in mammals. An additional possibility raised by the findings of Swann et al. (2014) is whether the presence of effective B cell development in the primordial thymus could have benefitted aspects of

intrathymic T cell development. In mammals, B cells have been linked to the negative selection of autoreactive T cell specificities in the establishment of T cell tolerance (Perera et al., 2013). Additionally, they can express tumor necrosis factor superfamily (TNFSF) ligands that regulate thymic microenvironments (Anderson and Takahama, 2012). Thus, the development and organization of the bifunctional thymus might have benefitted from signals from both lymphocyte development programs.

Despite their important findings, Swann et al. (2014) do not tackle the relationship between alterations in the lymphopoietic capacity of the thymus and the nature of thymus colonizing lymphoid progenitors. This is important as the developmental properties of cells recruited to the thymus remain unclear (Zhang and Bhandoola, 2014). For example, while studies report thymus colonization by progenitors with restricted lineage potential, others detect

the presence of common lymphoid progenitors. Thus, as with studies in mice, the ability of the ancient thymus to act as a site that either imposes, or reveals, T lineage commitment remains unclear.

In summary, Swann et al. (2014) provide a glimpse of the evolutionary history of the thymus. Reconstruction of the primordial thymus as a bipotent tissue that supports both T and B lymphopoiesis underlines similarities in the developmental programs of both cell types and identifies how alterations in TEC gene expression led to the effective and highly specialized thymic tissue seen in modern vertebrates.

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